

In the Claims

1-55. (Canceled)

56. (Currently amended) ~~An IL-7 drug substance comprising, as the active product, an IL-7~~  
A composition of matter comprising a human or simian IL-7 conformer, wherein said conformer  
comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-  
6 (Cys47-Cys141), wherein the total amount by weight of said IL-7 conformer in said ~~drug substance~~  
composition of matter is at least 98% by weight and wherein said ~~drug substance~~ composition of  
matter is substantially free of IL-7 molecular variants or product related impurities.

57. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim  
56, wherein said IL-7 conformer is a recombinant human IL-7 conformer.

58. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim  
57, wherein said IL-7 conformer comprises the amino acid sequence of SEQ ID NO: 2 or 4.

59. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim  
56, wherein said IL-7 conformer is a recombinant simian IL-7 conformer.

60. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim  
59, wherein said IL-7 conformer comprises the amino acid sequence of SEQ ID NO: 12.

61. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim  
56, wherein said IL-7 conformer is not glycosylated.

62. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim  
56, wherein said IL-7 conformer is glycosylated.

63. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim 56, wherein said IL-7 conformer is associated to the hepatocyte growth factor as a heterodimer.

64. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim 56, wherein said IL-7 conformer is functionally attached to a Fc portion of an IgG heavy chain through a peptide hinge region, said IgG being a human IgG1 or IgG4.

65. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim 56, wherein said IL-7 conformer is functionally associated to a Human Serum Albumin (HSA) or a portion of HSA as a fusion protein.

66. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim 56, said drug substance being substantially free of ~~an other~~ another IL-7 conformer.

67. (Currently amended) ~~IL-7 drug substance~~ The composition of matter according to claim 56, wherein the total amount by weight of IL-7 in said drug substance is at least 99.5% by weight.

68. (Currently amended) A pharmaceutical composition comprising an effective amount of a human or simian IL-7 conformer, wherein said conformer comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein at least 98% of the total amount by weight of IL-7 consists of said conformer and wherein said composition is substantially free of IL-7 molecular variants or product related impurities ~~a drug substance according to claim 56~~ and one or more pharmaceutically acceptable carriers.

69. (Currently amended) The pharmaceutical ~~Pharmaceutical~~ composition according to claim 68, wherein the pharmaceutically acceptable carrier is selected from sucrose, trehalose and an amino acid.

70. (Currently amended) ~~The pharmaceutical~~~~Pharmaceutical~~ composition according to claim 69, wherein the pharmaceutically acceptable carrier is contained in an appropriate buffer to form an isotonic solution.

71. (Currently amended) ~~The pharmaceutical~~~~Pharmaceutical~~ composition according to claim 70, wherein said appropriate buffer has a pH range ~~comprised of~~ between 5 to 7.5.

72. (Currently amended) ~~The pharmaceutical~~~~A-pharmaceutical~~ composition according to claim 71, wherein said appropriate buffer is an organic salt selected from a sodium citrate buffer ~~and/or~~ an ammonium acetate buffer.

73. (Currently amended) ~~The pharmaceutical~~~~A-pharmaceutical~~ composition according to claim 68, wherein said composition is a lyophilized form.

74. (Currently amended) ~~The pharmaceutical~~~~A-pharmaceutical~~ composition according to claim 68, wherein said composition further comprises a protein or a surfactant.

75. (Currently amended) ~~The pharmaceutical~~~~A-pharmaceutical~~ composition according to claim 68, further comprising an immuno-stimulating agent selected from a hematopoietic cell growth factor, a cytokine, an antigen and an adjuvant, or a combination thereof, for combined, separate or sequential use.

76. (Currently amended) ~~The pharmaceutical~~~~A-pharmaceutical~~ composition according to claim 75, wherein said hematopoietic cell growth factor is selected from the Stem Cell Factor (SCF), particularly the soluble form of the SCF, G-CSF, GM-CSF, Flt-3 ligand, IL-15 and IL-2.

77. (Currently amended) ~~The pharmaceutical~~~~A-pharmaceutical~~ composition according to claim 75, wherein the cytokine is selected from  $\gamma$  interferon, IL-2, IL-12, RANTES, B7-1, MIP-2 and MIP-1 $\alpha$ .

78. (Currently amended) ~~The pharmaceutical~~A pharmaceutical composition according to claim 75, wherein said antigen is selected from a synthetic or natural peptide, a recombinant protein, a killed, inactivated or attenuated pathogen product, a lipid, a portion thereof and a combination thereof.

79. (Currently amended) ~~A pharmaceutical~~The pharmaceutical composition according to claim 78, wherein said antigen is selected from antigens derived from HIV, Varicella Zoster virus, Influenza virus, Epstein Barr virus, type I or 2 Herpes Simplex virus, human cytomegalovirus, Dengue virus, ~~Hepatitis~~Hepatitis A, B, C or E virus, ~~Synectium-respiratory~~Respiratory Syncytium virus, human papilloma virus, mycobacterium tuberculosis, Toxoplasma and Chlamydia.

80. (Currently amended) ~~The pharmaceutical~~A pharmaceutical composition according to claim 75, wherein said adjuvant is selected from any substance, mixture, solute or composition facilitating or increasing the immunogenicity of an antigen and able to induce a Th1-type immune response, ~~such as CpG, QS21, ISCOM and monophosphoryl lipid A.~~

81. (Currently amended) ~~The pharmaceutical~~Pharmaceutical composition according to claim 68, for administration to a human patient for prophylactic or therapeutic stimulation of B or T lymphocyte development and proliferation, or for enhancement of global or specific immunoreconstitution, or for enhancement of humoral or cellular immune response.

82. (Currently amended) ~~The pharmaceutical~~A pharmaceutical composition according to claim 68, to prevent or reduce opportunistic infections in immunodeficient patients.

83. (Currently amended) ~~The pharmaceutical~~A pharmaceutical composition according to claim 68, to prolong lymphopoiesis stimulation or to produce specific immune response or to broaden the repertoire of a specific immune response in human patients.

84. (Currently amended) ~~The pharmaceutical~~ A pharmaceutical composition according to claim 81, 82 or 83, wherein human patients are immunodeficient patients, cancer patients, patients undergoing grafts, patients infected with a virus or a parasite, elderly patients or any patients having low CD4 count.

85. (Currently amended) ~~The pharmaceutical~~ A pharmaceutical composition according to claim 68, wherein the effective amount of ~~the drug substance is comprised~~ said IL-7 conformer is between about 3 to 300 µg/kg/day, preferably or between 10 to 100 µg/kg/day, and in particular administered from once daily, to twice or three times a week down to once weekly.

86. (Withdrawn) A nucleic acid molecule encoding an IL-7 polypeptide, wherein said nucleic acid molecule comprises an altered Shine-Dalgarno-like sequence.

87. (Withdrawn) A nucleic acid molecule comprising a sequence selected from SEQ ID Nos: 1, 3, 12, 16, 18, 20 or 22.

88. (Withdrawn) A vector comprising a nucleic acid according to claim 86.

89. (Withdrawn) A recombinant host cell comprising a nucleic acid according to claim 87 or a vector containing said nucleic acid.

90. (Withdrawn-currently amended) ~~A~~ The recombinant host cell according to claim 89, wherein said recombinant host cell is a human cell or a bacterial cell.

91. (Withdrawn-currently amended) ~~A~~ The recombinant host cell according to claim 90, which is *Escherichia coli* or *Bacillus Brevis*.

92. (Withdrawn-currently amended) A The recombinant host cell according to claim 90, which is a Chinese Hamster Ovary (CHO), HEK-293 cell line or a human stromal or epithelial cell line.

93. (Withdrawn) An antibody specifically immunoreactive with an IL-7 conformer as defined in claim 56.

94. (Withdrawn) A method of producing an IL-7 drug substance as defined in claim 56, the method comprising:

- a) providing a sample comprising IL-7 polypeptides,
- b) purifying an IL-7 conformer which comprises the following three disulfide bridges: Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47- Cys141) to produce an IL-7 drug substance, and
- c) optionally, measuring or quantifying, in the drug substance, said particular IL-7 conformer.

95. (Withdrawn-currently amended) The method ~~of~~ according to claim 94, wherein said sample is obtained from recombinant prokaryotic or eukaryotic host cells producing IL-7 polypeptides.

96. (Withdrawn-currently amended) The method ~~of~~ according to claim 95, wherein said sample is or derives from a culture of prokaryotic host cells encoding an IL-7 polypeptide and further wherein the method further comprises, prior to step b):

- i) treating said sample to cause a complete denaturation of said IL-7 polypeptides,
- ii) optionally purifying the denatured polypeptide obtained in step i) and
- iii) refolding the polypeptides.

97. (Withdrawn-currently amended) The method ~~of~~ according to claim 96, wherein step i) comprises the dissolution of inclusion bodies in a denaturant buffer.

98. (Withdrawn-currently amended) The method ~~of~~ according to claim 96, wherein step ii) is performed by hydrophobic chromatography, ion-exchange or inverse phase chromatography.

99. (Withdrawn-currently amended) The method ~~of~~ according to claim 97, wherein said hydrophobic chromatography is implemented using HIC butyl.

100. (Withdrawn-currently amended) The method ~~of~~ according to claim 96, wherein step ii) is carried out at a pH comprised between 6 and 9, preferably between 7 and 8,5 inclusive.

101. (Withdrawn-currently amended) The method ~~of~~ according to claim 96, wherein said purification step b) comprises the performance of an affinity chromatography.

102. (Withdrawn-currently amended) The method ~~of~~ according to claim 101, wherein said affinity chromatography is performed on a column of sulfated polysaccharides.

103. (Withdrawn-currently amended) The method ~~of~~ according to claim 102, wherein the sulfated polysaccharide is dextran sulfate or heparin.

104. (Withdrawn-currently amended) The method ~~of~~ according to claim 94, wherein the IL-7 conformer is characterized in the drug substance by Mass spectrometry, infra-red spectroscopy, NMR, by determining circular dichroism, by measuring the affinity toward a specific monoclonal antibody raised against said IL-7 conformer, or heparin affinity chromatography, and measured or quantified by ELISA, bioassay or the affinity of said IL-7 conformer for IL-7 receptor and any method of protein quantification if applied to the isolated conformer.

105. (Withdrawn) A method of controlling an IL-7-containing preparation, comprising determining the presence and/or relative quantity, in said preparation, of an IL-7 conformer as defined in claim 56.

106. (Withdrawn) A method of producing an IL-7 drug substance or pharmaceutical composition, said method comprising (i) culturing a recombinant host cell encoding an IL-7 polypeptide, (ii) isolating said recombinant polypeptide to produce an IL-7 drug substance and (iii) optionally, conditioning said IL-7 drug substance to produce a pharmaceutical composition suitable for therapeutic or vaccine use, said method further comprising a step of identifying, characterizing or measuring, in said drug substance or pharmaceutical composition, the quantity and/or quality of an IL-7 conformer as defined in claim 56 and, more preferably, a step of selecting the drug substance or pharmaceutical composition which comprises, as the active ingredient, more than about 98% of said IL-7 conformer.

107. (Withdrawn-currently amended) A The method according to claim 95, wherein IL-7 expression by the recombinant host cells is inducible, regulated or transient, so that the cell culture and IL-7 expression phases can be dissociated.

108. (Withdrawn-currently amended) The method ~~of~~ according to claim 106, wherein the quantity and/or quality of said IL-7 conformer is determined by mass spectrometry-related methods, with or without tryptic digest, circular dichroism, NMR, specific monoclonal antibody analysis for disulfide bridges and/or conformation characterization.

109. (Withdrawn) A method for inducing a prolonged lymphopoiesis stimulation or for amplifying an immune response in a subject, comprising administering to a subject in need thereof an effective amount of an IL-7 drug substance obtained by a method according to claim 94.

110. (Withdrawn) A method for preventing or treating a disease associated with an immunodeficiency, comprising administering to a subject in need thereof an effective amount of an IL-7 drug substance obtained by a method according to claim 94.



111. (New) The composition of matter according to claim 56, wherein said IL-7 conformer is a human IL-7 conformer.

112. (New) The composition of matter according to claim 56, wherein said IL-7 conformer is a simian IL-7 conformer.

113. (New) The pharmaceutical composition according to claim 68, wherein said IL-7 conformer is a human IL-7 conformer.

114. (New) The pharmaceutical composition according to claim 68, wherein said IL-7 conformer is a simian IL-7 conformer.